REMARKS

Claims 1-19 are pending.

Applicants thank the Examiner for withdrawing the prior objection to the specification relating to SEQ ID NOS:66 and 67 and for favorable consideration of Applicants' submitted Declaration by Dr. Peter Laird.

Applicants additionally thank the Examiner for withdrawing the prior rejection under 35 U.S.C. § 112 first paragraph, for alleged new matter.

Applicants acknowledge the Examiner's maintained rejection of claims 1-3, 5-8 and 10, under 35 U.S.C. § 102(b), as allegedly being anticipated by *Iacopetta*, as defined by *Kyrgidis* et al., and of claims 15-19, under 35 U.S.C. § 103(a), as being unpatentable over *Iacopetta*, as defined by *Kyrgidis* et al., in view of Huang et al. Applicants have amended independent claim 1 to obviate these rejections. Claims 2, 4, 5, 9, 10 and 18 have been cancelled herein in view of Applicants' amendments to independent claim 1.

Applicants acknowledge the Examiner's new grounds of rejection of claims 1-19, under 35 U.S.C. § 112, first paragraph, as allegedly being insufficiently enabled. Applicants have amended independent claim 1 and provide attendant rebuttal argument in the context of the claim amendments to obviate this rejection.

Applicants acknowledge the Examiner's new grounds of rejection of claims 1-19, for provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10/240,126. Applicant's respectfully traverse this rejection, based on the fact that the claims of the '126 Application have been limited to ESR1 gene sequences in response to a prior restriction election.

No new matter has been added.

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FORMALITIES

Priority. Applicants understand from the record that all claims are awarded the benefit of the date of the provisional filing (*i.e.*, 31 March 2000).

Rejections under 35 U.S.C. § 102 and

35 U.S.C. § 103

The Examiner has maintained the rejection of claims 1-3, 5-8, 10 and 20, under 35 U.S.C. § 102(b), as allegedly being anticipated by *Iacopetta* et al., (*Int. J. of Cancer*, 17:429-432, 1997), as defined by *Kyrgidis* et al., (*J. of Surgical Research*, 125:189-212, 2005), and has further maintained the rejection of claims 15-19, under 35 U.S.C. § 103(a), as being unpatentable over *Iacopetta*, as defined by *Kyrgidis* et al., in view of Huang et al (*Human Molecular Genetics*, 8:459-470, 1999).

Specifically, applicants recitation of "esophageal cancer related condition," in the preamble of claim 1 has been interpreted by the Examiner to encompass colorectal cancer (as taught by *Kyrgidi*), and the Examiner further alleges that Iacopetta teaches regional hypermethylation of a 3' downstream region of MYOD1 in relation to colorectal neoplasia, and thus teaches diagnosis or prognosis thereof.

Applicants, have amended claim 1 to obviate this rejection by deleting recitation of "esophageal cancer related condition." No new matter has been added.

Applicants, therefore, respectfully request withdrawal of the 35 U.S.C. § 102(b)-based rejection of claims 1-3, 5-8, 10 and 20, and the 35 U.S.C. § 103(a)-based rejection of claims 15-19, based on applicants' above described amendment to independent claim 1.

Rejections under 35 U.S.C. § 112 ¶1

Enablement

The Examiner has maintained the rejection of claims 1-19, under 35 U.S.C. § 112 ¶1, for alleged lack of enablement.

Specifically, the Examiner alleges **(A)** that "the specification, while being enabling for a method of diagnosing or prognosing of esophageal cancer, esophageal dysplasia, esophageal metaplasia, or Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof, comprising obtaining a sample of esophageal tissue comprising genomic DNA, performing a methylation assay of the tissue sample wherein the methylation assay determines the methylation state of the sequence of MYOD1 delimited by the primer pair of SEQ ID NO:7 and 8 as compared to normal control DNA sample, and diagnosing or prognosing esophageal cancer, esophageal dysplasia, esophageal metaplasia, or Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof, based, at least in part, on the detection of hypermethylation of the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NO:7 and 8 as compared to normal control DNA sample, does not reasonably provide enablement for diagnosis or prognosis of esophageal cancer, esophageal dysplasia, esophageal metaplasia, or Barrett's intestinal tissue, Barrett's esophagous, precancerous conditions in normal esophageal squamous mucosa or combinations thereof, or any esophageal cancer related condition by detecting hypermethylation, or determining the hypermethylation state of, in 'at least one' CpG sequence in any region of the MYOD1 gene" (Office Action of 04 May 2006, at page 4).

The Examiner further states that **(B)** the claims "continue to broadly encompass diagnosis based on *any* methylation state" (*Id*, at page 5).

The Examiner further states that **(C)** while the specification "provides an association between hypermethylation of CpG islands in the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NOS:7 and 8, the specification provides no predictable correlation that the methyaltion status of any single CpG dinucleotide in *any* region of the MYOD1 gene, would be diagnostic or prognostice of *any* disease...." (*Id*, at page ;7). Additionally, the Examiner cites Toyota (Toyota et al., Cancer Research, 59:4535-4541, September 1999) for the proposition that that the "art does not support the idea that all contiguous CpG islands are associated with cancer." Specifically, the Examiner urges that Toyota teaches that different CpG island regions behave

differently, and that "the skilled artisan would be unable to predict whether other CpG islands in the MYOD1 gene act in an independent manner."

(A):

With respect to the Examiner's contention **(A)** above, Applicants have responsively amended *independent* claim 1 by deleting recitation of "esophageal cancer related condition" in the preamble, by deleting "pre-cancerous conditions in normal esophageal squamous mucosa" from the language of step (c), to appropriately conform the claim elements as suggested by the Examiner.

(B):

With respect to the Examiner's contention **(B)** above, Applicants have responsively amended *independent* claim 1 by reciting "detection of hypermethylation of the at least one genomic CpG sequence." Support for this amendment is found throughout the originally filed specification, and in particular, for example, in original claim 20 and the working Examples.

(C):

With respect to the Examiner's contention **(C)** above, Applicants first respectfully note that the Examiner has inadvertently misconstrued Toyota et al. Citing Toyota et al., the Examiner essentially states that the art and teachings do not support the idea that all contiguous CpG islands are associated with a particular cancer ("behave independently"). The Examiner urges that Toyota teaches a detailed analysis of CpG islands within the CACNA1G gene, stating that Toyota teaches "eight regions, each behaving differently" (regions 1 and 2 being concordant, regions 5, 6 and 7 behaving differently than regions 1-3, and regions 4, and 8 behaving differently again). The Examiner thereby concludes that "with respect to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to behave independently" (citing page 4535-4541), and "given the lack of guidance in the specification as to other regions in the MYOD1 gene which contain hypermethylated CgG islands diagnostic or prognostic for the conditions set forth in the claims, the

skilled artisan would be unable to predict whether other CpG islands in the MYOD1 gene act in an independent manner."

Applicants agree with the Examiner that Toyota teaches "examples where CpG islands act independently" of each other. However, Applicants' teaching and disclosure is that CpG dinucleotide sequences *within* a given CpG island behave coordinately, and here, the teachings of Toyota are consistent with, and support the applicants' currently amended claims.

Specifically, Toyota initially describes/defines a large 4Kb region (Toyota at pate 4536 column 2 middle of 1st full para), and divides this 4kb region into 8 subregions. However, Toyota notes that this region is considerably larger that typical CpG islands (Toyota at page 4537, column 2, 1st full para), and it is explicitly concluded that "with regards to hypermethylation in cancer, the CpG-rich region upstream of CACNA1G appears to be composed of two CpG islands that behave independently" (MINT31 regions 1 and 2 corresponding to the upstream CpG island 1; the 5' regions 5-7 of CACNA1G in the downstream CpG island 2; and regions 3, 4 and 5 between CpG island 1 and 2, behaving differently. Toyota concludes (page 4540, at end of carryover para) that "methylation of MINT 31 appears to be independent of methylation of CACNA1G, suggesting that they are two distinct CpG island regulated by different mechanisms." Significantly, therefore, Toyota teaches that while different CpG islands within a gene area can behave differently or independently, the subregions within a given larger CpG rich region, for example regions 1 and 2 of island 1 and regions 5-7 of island 2, ***behave coordinately*** and define the behavior of the CpG island which comprises the subregions. Therefore, Toyota like the bulk of art in this area, is fully consistent with the teachings of the present invention which teach that the CpG dinucleotides within a given contiguous CpG island are coordinately methylated.

The instant specification has taught that a predictable correlation exists between esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof, and hypermethylation of a particular region (and particular CpG dinucleotides) of a single CpG island corresponding to a 200 bp MYOD1 promoter region CpG island sequence SEQ ID NO:66 that encompasses primer SEQ ID NOS:7 and 8, and that has

both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5 (that extends from nucleotide position 9,843 to 10,043 of SEQ ID NO:66).

Therefore, in view of the Examiner's comments, Applicants have responsively amended *independent* claim 1 by reciting "wherein the genomic CpG sequence is located within the *MYOD1* gene CpG island sequence having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5 that extends from nucleotide position 9,843 to 10,043 of SEQ ID NO:66." Support for this amendment is found throughout the originally filed specification, for example at page 7, line 35 to page 8, line 6, (defining the size, e.g. 200 to about 2 Kb, and base composition, etc., of CpG islands), at page 28, line32, 33, and page 30, TABLE II (describing the CpG content etc of a 200 bp CpG island encompassing primers SEQ ID NOS:7 and 8) (see also Appendix A, attached hereto showing the distribution of CpG islands in the MYOD1 SEQ ID NO:66, according to Applicants disclosed criteria, and showing the instant CpG island extending from nucleotide position 9,843 to 10,043 of SEQ ID NO:66, as derived using the EMBOSS program cpgplot to plot CpG rich areas, and cpgreport to report all CpG rich regions).

Claims 2, 4, 5, 9, 10 and 18 have been cancelled herein in view of Applicants' amendments to independent claim 1.

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, applicants contend that it would not require undue experimentation for a person of skill in the art to practice the invention as claimed. Therefore, with respect to **(C)**, and in the context of presently amended claim 1, the specification is enabling for making and using the full scope of the claimed subject matter.

Applicants, therefore, respectfully request withdrawal of the Examiner's rejection of claims 1-19, under 35 U.S.C. § 112 ¶1, in view of applicants above described claim amendments.

Nonstatutory Double Patenting Rejection

The Examiner has rejected claims 1-19, under new grounds for provisional nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-20 of copending Application No. 10/240,126.

Applicants respectfully traverse this rejection, based on the fact that the claims of the '126 Application have been limited to ESR1 gene sequences in response to a prior restriction election.

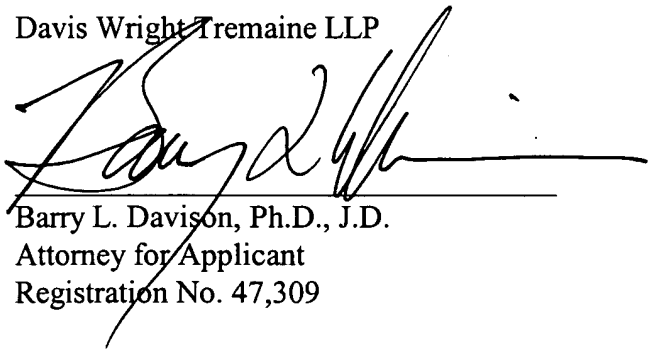
Applicants, therefore, respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request entry of the present Response and Amendment, and allowance of all pending claims. The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

Respectfully submitted,

Davis Wright Tremaine LLP



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APPENDIX B

CpG islands within the MYOD1 SEQ ID NO:66 according to applicants' disclosed criteria:

Observed/Expected ratio > 0.60
Percent C + Percent G > 50.00
Length > 200

CpG island length (bp) and nucleotide position within SEQ ID NO:66:

Length 277 (2038..2314)

Length 201 (9843..10043)

Length 819 (10346..11164)

Length 203 (11465..11667)

Length 344 (11845..12188)

Length 226 (12201..12426)